REMARKS

Status of the Claims

Pending claims

Claims 31 to 42 and 53 to 88 are pending (claims 1 to 30 and 43 to 52 have been canceled).

Claims amended and added in the instant amendment

In the present response, claims 31, 53, 65 and 77 are amended; and new claims 89 to 97 are added. Thus, after entry of the instant amendment, claims 31 to 42 and 53 to 97 will be pending and under examination.

Both before and after the above changes and cancellations, and the addition of new claims, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq*. The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents.

Outstanding Rejections

Claims 31 to 42 and 53 to 88 are rejected under 35 U.S.C. §112, second paragraph. Claims 31 to 42 and 65 to 88 are rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. Support for claims directed to methods comprising screening for variants having a polymerase activity can be found, , *inter alia*, on page 23, lines 16 to 32. Support for claims directed to methods comprising generating a thermostable polymerase activity at, e.g., a temperature in a range from about 95°C to 113°C, can be found, *inter alia*, on page 3, lines 6 to 21, page 5, lines 21 to 25, and page 6, lines 31 to 32, of the specification. Support for claims directed to methods comprising generating a polymerase having a 3'→ 5' exonuclease activity can be found, *inter alia*, on page 7, lines 4 to 17, of the specification. Support for claims directed

to methods comprising generating a polymerase that can function under conditions of high salinity can be found, *inter alia*, on page 23, lines 1 to 15. Support for claims directed to methods wherein the nucleic acid encoding a polymerase has a high guanidine-cytosine (GC) content can be found, *inter alia*, on page 23, lines 30 to 32. Support for claims directed to methods comprising generating a polymerase capable of amplifying a template sequence during PCR amplification procedures can be found, *inter alia*, on page 8, lines 2 to 4. Support for claims directed to methods comprising obtaining a nucleic acid comprising a sequence having at least 50%, 60%, 70%, 80%, 90 to 95% sequence identity to the sequence set forth in SEQ ID NO:1 and encoding a polypeptide having a polymerase activity can be found, *inter alia*, on page 14, lines 16 to 24. Applicants submit that no new matter is introduced by the present amendments.

Issues under 35 U.S.C. §112, second paragraph

Claims 31 to 42 and 53 to 88 are rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard and the invention. The Office alleges that claims 31 to 42 and 53 to 88 are missing an essential step, a selection step in which the generated variant is tested or screened such to determine which of the generated variants encode a polypeptide having a polymerase activity.

Applicants respectfully traverse, noting that the claims are directed to methods of generating a nucleic acid encoding a variant that encodes a polypeptide having a polymerase activity, not methods for identifying or isolating a variant that encodes a polypeptide having a polymerase activity. However, merely to expedite prosecution, the instant amendment addresses this issue.

Issues under 35 U.S.C. §112, first paragraph

Written Description

Claims 31 to 42 and 65 to 76, and 77 to 88 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Patent Office notes that the instant specification sufficiently described the claimed methods of generating a variant of SEQ ID NO:1. However, it is alleged that a description of a single species is not sufficient to describe a genus defined as having 70% sequence identity to SEQ ID NO:1.

Applicants respectfully submit that the claimed invention is sufficiently described in the specification so that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants' were in possession of the claimed invention at the time of filing. Applicants respectfully submit that describing a genus of polynucleotides in terms of its physico-chemical properties (e.g., sequence identity) and function (e.g., encoding a polymerase) satisfies the written description requirement of section 112, first paragraph.

Applicants respectfully refer to the USPTO guidelines concerning compliance with the written description requirement of U.S.C. §112, first paragraph. In example 14 of the guidelines (a copy of which is attached as Exhibit A), a claim reciting variants claimed by sequence identity to a sequence is sought (specifically, "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B). In the example, the specification is described as providing SEQ ID NO:3 and a function for the protein. The specification contemplates, but does not exemplify variants of SEQ ID NO:3 that can have substitutions, deletions, insertions and additions. Procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art and an assay is described which will identify other proteins having the claimed catalytic activity. The analysis of example 14 states that procedures for making variants (which have 95% sequence identity) are conventional in the art. The Guidelines conclusion states that the disclosure meets the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention.

Analogously, the genus of nucleic acids used in the claimed methods is described by structure (the exemplary nucleic acid SEQ ID NO:1), a physico-chemical property (percent sequence identify) and function (having a polymerase activity). All nucleic acids of the claimed genus must have at least 70% or more sequence identity to a sequence as set forth SEQ ID NO:1. The USPTO guidelines recognize that written description is met for a genus of polypeptides

described by structure, a physico-chemical property (e.g., a % sequence identity) and a defined function, the genus of claimed polypeptides also meet the written description requirements of section 112.

The genus of nucleic acids used in the claimed methods also fully comply with the requirements for written description of a genus of nucleic acids as set forth in University of California v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed. Cir. 1997). In Lilly, the Court stated that, "[a] description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs....*or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.*" (emphasis added) Lilly, 43USPQ2d at 1406. As noted above, the instant claims clearly set forth specific structural and physical characteristics of the claimed polymerase-encoding nucleic acids. The claimed genus of polypeptides all must have a polymerase activity and a specific physical characteristic, e.g., a % sequence identity to the exemplary nucleic acid. Therefore, the genus of nucleic acids used in the claimed methods is defined via shared physical and structural properties in terms that "convey with reasonable clarity to those skilled in the art that Applicant, as of filing date sought, was in possession of invention." (Vas-Cath Inc. V. Mahukar, 19 USPQ2d 1111, (Fed Cir. 1991)).

More recently, the Federal Circuit stated

> Similarly, in this court's most recent pronouncement, it noted:
>
> > More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.
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> Amgen, 314 F.3d at 1332 [Amgen Inc. v. Hoechst Marion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003)].

Moba, B.V. v. Diamond Automation, Inc., 2003 U.S. App. LEXIS 6285; Fed. Cir. 01-1063, -1083, April 1, 2003.

Analogously, the function of the polymerases encoded by the nucleic acids used in the claimed methods is sufficiently correlated to a particular, known structure (the exemplary sequences) and a physical (physico-chemical) property (percent sequence identity).

Accordingly, the sequences used in the claimed methods are defined via shared physical and structural properties in terms that convey with reasonable clarity to those skilled in the art that Applicants, as of the filing date and at the time of the invention, were in possession of the claimed invention.

Applicants also respectfully note that claims directed to a genus of polypeptide-encoding nucleic acids as described and enabled by the specific physical characteristic of percent sequence identity or stringent hybridization and function have been issuing from the USPTO recently and for many years, see, e.g., U.S. Patent Nos. 6,541,684; 6,541,236; 6,541,220; 6,534,309; 6,492,150; 6,465,210; 6,413,522; 6,384,304; 6,342,657; 6,274,790 (selected claims from these patents are attached as Exhibit B). See also the recently issued claims directed to, e.g., 72.5% sequence identity, as in USPN 6,593,514; 75% sequence identity, as in USPN 6,586,215; 80% sequence identity, as in USPN 6,596,926; 85% sequence identity, as in USPN 6,590,141 and USPN 6,586,179; 86% sequence identity, as in USPN 6,583,337; 90% sequence identity (and "stringent hybridization"), as in USPN 6,541,684 (claims attached as Exhibit C).

Accordingly, Applicants respectfully submit that the pending claims meet the written description requirement under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

Enablement

Claims 65 to 88 are rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Patent Office notes that the specification is enabling for a method of generating a polymerase variant comprising obtaining a nucleic acid comprising SEQ ID NO:1 and sequences complementary thereto, and modifying, deleting or adding one or more nucleotides in said sequence, wherein the variant maintains polymerase activity.

However, it is alleged that the specification does not reasonably provide enablement for any method of generating a variant. The Patent Office notes that claims 65 to 88 are so broad as to encompass any method of generating any variant that encodes a polymerase. It

is alleged that the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claims (see page 6 of the office action).

Applicants acknowledge that the claimed methods encompass any method for generating a change, or variation, in a nucleic acid sequence. However, Applicants respectfully aver that methods for changing, or varying, nucleic acids sequences were well known in the art at the time of the invention. The specification describes several exemplary protocols for changing, or varying, nucleic acids sequences that can be used in the methods of the invention, for example, error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, sexual PCR mutagenesis, in vivo mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis, site-specific mutagenesis, ligation reassembly and gene site saturated mutagenesis (GSSM).

There is no requirement under the law that every possible way of carrying out an invention be expressly described. A patent applicant is not required to identify every possible variation or embodiment of his or her invention. See, e.g., Utter v. Hiraga, 845 F.2d 993, 998-99, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of Section 112 Para. 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."). As noted by Judge Rich in In re Gay, 309 F.2d 769, 774, 135 USPQ 311, 316 (CCPA 1962), furthermore, it is the law that, "Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." See also Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1532, 20 USPQ2d 1300, 1302 (Fed. Cir. 1991) (a patent is not a "production specification").

As long as the invention is disclosed in such a manner to allow one skilled in the art to practice the invention without undue experimentation, the enablement requirement is fulfilled. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). MPEP §2164.01.

The Patent Office also alleges that the specification does not enable the claimed invention because the disclosure gives no guidance beyond the structure of SEQ ID NO:1 as to how one would obtain and/or modify the polynucleotides of SEQ ID NO:1 to obtain a variant polymerase, and it is not routine in the art to screen for multiple substitutions or multiple modifications (see office action, page 7, lines 12 to 14).

However, as declared by Dr. Walter Callen (see attached Rule 132 declaration, Exhibit D), an expert in the field of molecular biology, it was considered routine by one skilled in the art at the time of the invention to screen for multiple substitutions or multiple modifications in a nucleic acid sequence for functional variations, e.g., variant nucleic acids that encode a polymerase enzyme. For example, by 1996, high through-put *in vivo* (e.g., whole cell) nucleic acid expression and screening protocols were well known in the art. In particular, high through-put methods for screening for polymerase activity, such as polymerase chain reaction (PCR), were well known in the art. Accordingly, at the time of the invention it would have been considered routine by one skilled in the art to screen for multiple substitutions or multiple modifications in a nucleic acid sequence for functional variations.

The Patent Office alleges that because the specification does not establish, inter alia, regions of protein structure which may be modified without effecting function or activity and a rational and predictable scheme for modifying any nucleic acid of SEQ ID NO:1 (see the paragraph spanning pages 7 and 8 of the office action), the specification provides insufficient guidance as to which variation will be successful. It is also alleged that because the specification provides insufficient guidance as to which variation will be successful, it would take undue experimentation to determine which substitutions will be acceptable.

Applicants respectfully aver that whether the methods of the invention use stochastic (random) or non-stochastic (non-random, e.g., directed evolution) means to generate nucleic acid variations, it would only requirement routine screening, and not undue experimentation, to make and select variant polymerase-encoding nucleic acids.

The Patent Office is alleging that making, and then screening, large numbers of nucleic acid sequences to identify variant polymerase-encoding nucleic acids is not routine experimentation. In fact, whether large numbers of compositions (e.g., antibodies, nucleic acids or proteins) must be screened to determine if one is within the scope of the claims is irrelevant to

an enablement inquiry. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit. The Federal Circuit in In re Wands directed that the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation. The court set forth specific factors to be considered.

One of these factors is "the quantity of experimentation necessary." Guidance as to how much experimentation may be needed and still not be "undue" was set forth by the Federal Circuit in, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). An applicant had claims that were generic to all IgM antibodies directed to a specific antigen. However, only a single antibody producing cell line had been deposited. The PTO had rejected claims that were generic to all antibodies directed to the antigen as lacking an enabling disclosure.

The Federal Circuit reversed, noting that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicants' written disclosure, produce and screen new hybridomas secreting other monoclonal antibodies falling within the genus without undue experimentation. The court held that applicants' claims need not be limited to the specific, single antibody secreted by the deposited hybridoma cell line (significantly, the genus of antibodies was allowed even though only one antibody specie was disclosed). The court was acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation.".

Analogously, those skilled in the relevant art (molecular biology) at the time of the instant claimed invention could, using the state of the art and applicants' written disclosure, produce and screen variant nucleic acids for polymerase activity without undue experimentation. Practitioners in the art at the time of the invention were prepared to make and screen large numbers of negatives in order to find a sample with the desired properties, e.g., a polymerase-encoding nucleic acid. Thus, the making and screening that would be necessary to generate polymerase-encoding nucleic acids, as set forth in the claimed methods, was not "undue experimentation."

In light of the amendments and arguments presented herein, Applicants respectfully request reconsideration and withdrawal of the rejection based upon 35 U.S.C. §112, first paragraph.

Applicants also respectfully note that claims directed to a genus of polypeptides as described and enabled by the specific physical characteristic of stringent hybridization and function have been issuing from the USPTO recently and for many years, see, e.g., U.S. Patent Nos. 6,541,684; 6,541,236; 6,541,220; 6,534,309; 6,492,150; 6,465,210; 6,413,522; 6,384,304; 6,342,657; 6,274,790 (selected claims from these patents are attached as Exhibit B).

CONCLUSION

Applicants request that the Examiner reconsider the application and claims in light of the foregoing reasons and amendments and respectfully submit that the claims are in condition for allowance.

If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues and to work with the Examiner toward placing the application in condition for allowance.

If any necessary additional such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-1050. Overcharges can be credited to the same account.

Respectfully submitted,

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